REMARKS

Claims 8, 14, 16 and 18 are pending in this application. The claims are amended herein only to address the objections set forth in the Claim Objections section of the Office Action.

Reconsideration of the application is respectfully requested based on the following.

Claim Objections

Several objections to the claims are set forth in the Office Action, to which Applicants respond as follows.

Claim 16 is objected to as being of improper dependent form for failing to limit the subject matter of claim 8. Applicants respectfully disagree. The alleged basis for this objection is that claim 8 recites that the binding complex is delivered from an extracellular environment, and that this is inconsistent with claim 16 which recites that the binding complex can be delivered *in vitro* or *in vivo*. Applicants respectfully submit there is no inconsistency. Claim 8 recites whence comes the binding complex, i.e., it is delivered from an extracellular environment, such as outside the target cell. Claim 16 recites where goes the binding complex, i.e., into cells, and those target cells may be cultured *in vitro*, i.e., in a test tube, or may be *in vivo*, i.e., in a living organism. Thus, there is no inconsistency. Applicants respectfully request withdrawal of this objection.

Claims 8, 14, 16 and 18 are objected to for a number of very minor article omissions. These objections are addressed in the amended claims. Applicants respectfully request withdrawal of this objection.

Rejections of Claims over Ye et al. in view of Korsmeyer et al.

Claims 7-9 and 14 stand rejected as obvious over Ye et al. in view of Korsmeyer et al., US 2008/0097081. Applicants respectfully traverse this rejection for at least the following reasons.

The presently claimed invention includes a step of obtaining a binding complex outside a cell; and DNA binding domain(DBD) and DNA binding

sequence(DBS) for this step, and thereafter delivering the binding complex into the eukaryotic cytoplasm or nucleus. However, Ye et al., with or without Korsmeyer et al. fails to disclose or suggest any such steps, including a DBD or DBS.

Applicants incorporate by reference the previously submitted arguments and evidence. In addition, Applicants respectfully submit the following additional points.

In setting forth the rejections, the present Office Action stated:

> Ye et al (Phar. Res. 19(9): 1302-1309,2002, specifically pp. 1302-1305, Page 4 especially Fig. 1) teach a binding complex comprising a chimeric protein (protein fusion) comprising an HA epitope, a Gal4(OBO)-VP16 and a His tag. The chimeric protein can also include a Tat or VP22. Ye et al teach a vector (peptide transducing recombinant (PTO) expression vector) encoding the above complex, including a promoter, that is expressed in bacteria cells. The fusion protein is then purified and added to the medium of eukaryotic cells with a reporter plasmid encoding a luciferase gene linked to five tandem repeats of the Gal4 binding site (inducible promoter) (p. 1304-05). The fusion protein is transported into the cell, and binds to the reporter plasmid binds, completing the binding complex. See specifically Fig. 1. The vector encoding the chimeric protein can also contain a sequence encoding a nuclear localization sequence (p. 1303). However, while they teach extracellular delivery of the fusion protein, they do not teach extracellular delivery of the whole binding complex.

Applicants respectfully submit that this characterization of Ye et al., while technically correct, greatly oversimplifies the differences between the disclosure of Ye et al., taken as a whole, and the presently disclosed and claimed invention. When properly viewed as a whole, the asserted combination of Ye et al. with the disclosure of US 2008/0097081 is not something a person of ordinary skill in the art would have found obvious, for these references are focused on wholly different goals.

As stated in the previous Office Action, "Ye et al produce expression vectors of chimeric proteins incorporating the transcriptional activator and PTD, and tests the ability of the PTD to deliver the protein in a cell by luciferase activity in a cell which is already (i.e., has previously been) transfected with the Gal4-luciferase reporter vector." Thus, as recognized by the Examiner, the entire goal of Ye et al. is to test the ability of the PTD to deliver a protein into a cell, in which the cell has already been separately transfected with the Gal4-luciferase reporter gene. Ye et al. is not attempting, and to Applicants' understanding, does not in any way suggest, the possibility to obtain and isolate a fusion protein extracellularly, as recited in steps i)

and ii) of the present claims, and then to prepare a recombinant expression vector as recited in step iii) of the present claims, to combine the fusion protein with the recombinant expression vector to obtain a binding complex extracellularly, as recited in step iv) of the present claims, and thence to deliver the extracellular binding complex of step iv) into a eukaryotic cytoplasm or nucleus, as recited in step v) of the present claims. The entire purpose of Ye et al. is to test the ability to deliver a protein into a viable cell. As stated by Ye et al. at p. 1307, full paragraph, right column, "In the work described here we have used a reporter gene assay to evaluate different strategies for intracellular delivery of proteins." This statement bears out the first sentence in the Introduction on p. 1302, which clearly focuses on delivery of proteins intracellularly. The reporter gene was only used to test whether the protein was actually delivered into a viable cell, "because only healthy cells with intact membranes can engage in transcription and translation, and thus express the reporter gene, this assay unambiguously evaluates delivery of exogenous proteins into intact cells". See, p. 1304, first full paragraph, left column. Emphasis added. Thus, Ye et al. teaches and suggests nothing more than delivery of exogenous proteins into cells, and does not teach or suggest the possibility that an extracellularly obtained binding complex might be introduced into the eukaryotic cytoplasm or nucleus.

Therefore, Ye et al. has no interest and makes no suggestion to deliver a binding complex into a eukaryotic cytoplasm or nucleus, as in the present invention, and there would be no reason whatsoever for a person having ordinary skill in the art to even look to US 2008/0097081.

US 2008/0097081 relates to polypeptides for use in treating apoptosis. As noted in the Office action, at [0082] and [0083], this reference discloses a fusion protein which is a BID α6 peptide and BID mutein polypeptide-transduction domain fusion protein in which the BID α6 peptide and BID mutein polypeptide sequences comprise one or more domains that are fused to a protein transduction domain. When administered, the fusion protein inhibits an interaction between a BID α6 peptide and BID mutein polypeptide ligand and a BID α6 peptide and BID mutein polypeptide in a cell, to thereby suppress BID α6 peptide and BID mutein

polypeptide-mediated signal transduction *in vivo*. This disclosure relates to formation of a fusion protein, and might possibly correspond to step ii) of the present invention. However, there is no disclosure of which Applicants are aware that step i) is carried out, and there is no disclosure of which Applicants are aware that the fusion protein obtained by the reference would thereafter be used in a process including steps corresponding to steps iii), iv) and v) of the presently claimed invention. Therefore, US 2008/0097081 fails to remedy the shortcomings of Ye et al.

As with Ye et al., there is no suggestion in US 2008/0097081 to create and then to deliver a binding complex into a eukaryotic cytoplasm or nucleus, as set forth in the presently pending claims.

Thus, Applicants respectfully submit that even if, despite there being no reason or motivation to do so, one of ordinary skill in the art would try to combine the selected disclosures of Ye et al. and US 2008/0097081, that person would still not have been led to Applicants' claimed invention, and the combination would not have rendered obvious Applicants' claimed invention. This is so because the cited references fail to disclose all of the elements of the claimed invention. Having failed to indentify all of the elements of the claims in the prior art, the can be no *prima facie* case of obviousness, and so all of the rejections under Section 103 should be withdrawn.

Accordingly Applicants respectfully submit that the foregoing claim amendments, previously submitted evidence and the arguments herein and previously submitted clearly demonstrate that the presently claimed invention of claims 8, 14, 16 and 18 would not have been obvious. Therefore, Applicants respectfully request withdrawal of the asserted rejections and allowance of the claims. Notice to such effect is respectfully requested.

Conclusion

For the reasons set forth in the foregoing, Applicants respectfully submit that the present application is in condition for allowance, and an early notice to such effect is respectfully requested.

Should the Examiner consider that a telephone interview would be helpful to facilitate favorable prosecution of the above-identified application, the Examiner is invited to contact the undersigned at the telephone number provided below.

If any additional fees are required for the filing of this paper, Applicants request the Commissioner to charge the fees to deposit account #18-0988, Dkt. No. NAMNP0103US.

Respectfully submitted,
RENNER, OTTO, BOISSELLE & SKLAR, L.L.P.

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By: thomaswadams/
Thomas W. Adams
Reg. No. 35,047

1621 Euclid Avenue, 19th Floor
Cleveland, Ohio 44115
(216) 621-1113